

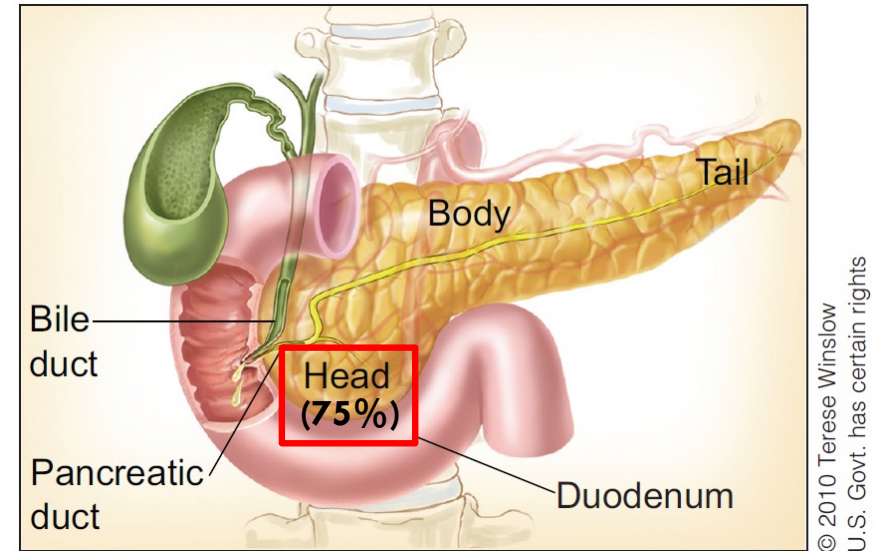
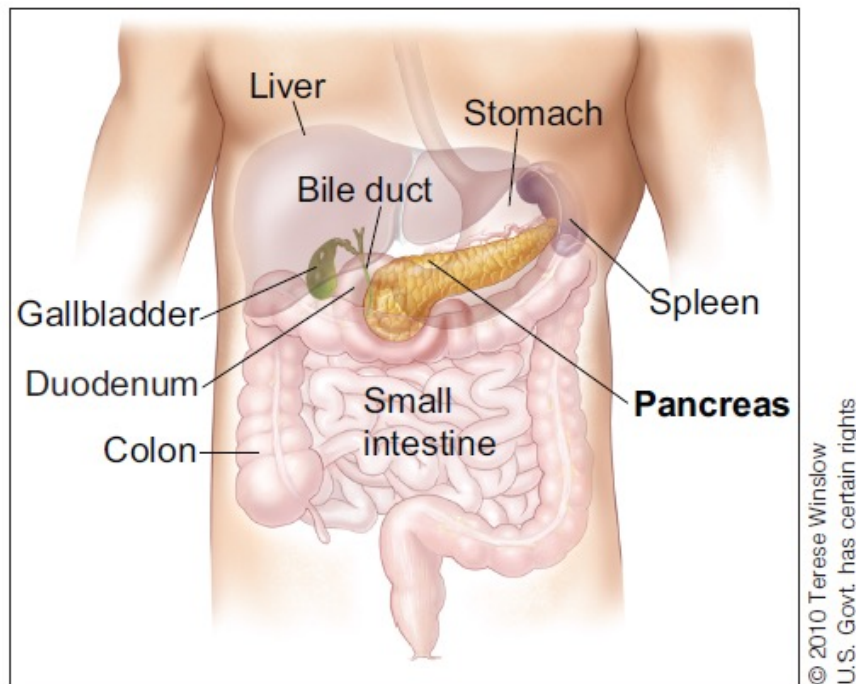


PANCREATIC CANCER AND INFLAMMATION

Demystifying Medicine

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February 21, 2017

PANCREAS CANCER



Subtypes

- Adenocarcinoma (~90%)
- Neuroendocrine (<5%)
- Mucinous
- Acinar Cell Carcinoma

RISK FACTORS FOR PANCREATIC CANCER

Risk for lung cancer in long term smokers is 8-15x

Ryan et al, *NEJM*, 2014
Jung et al, *Epidemiol. Health*, 2016

Table 1. Risk Factors and Inherited Syndromes Associated with Pancreatic Cancer.*

Variable	Approximate Risk
Risk factor	
Smoking ³	2–3
Long-standing diabetes mellitus ⁴	2
Nonhereditary and chronic pancreatitis ⁵	2–6
Obesity, inactivity, or both ⁶	2
Non-O blood group ⁷	1–2
Genetic syndrome and associated gene or genes — %	
Hereditary pancreatitis (<i>PRSS1</i> , <i>SPINK1</i>) ⁸	50
Familial atypical multiple mole and melanoma syndrome (<i>p16</i>) ⁹	10–20
Hereditary breast and ovarian cancer syndromes (<i>BRCA1</i> , <i>BRCA2</i> , <i>PALB2</i>) ^{10,11}	1–2
Peutz–Jeghers syndrome (<i>STK11</i> [<i>LKB1</i>]) ¹²	30–40
Hereditary nonpolyposis colon cancer (Lynch syndrome) (<i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i>) ¹³	4
Ataxia–telangiectasia (<i>ATM</i>) ¹⁴	Unknown
Li–Fraumeni syndrome (<i>P53</i>) ¹⁵	Unknown

* Values associated with risk factors are expressed as relative risks, and values associated with genetic syndromes are expressed as lifetime risks, as compared with the risk in the general population.

SYMPTOMS OF PANCREATIC CANCER

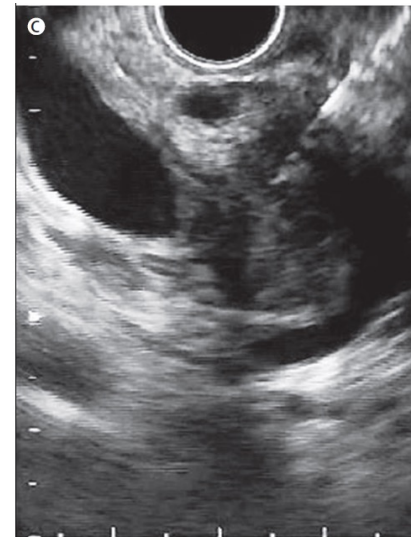
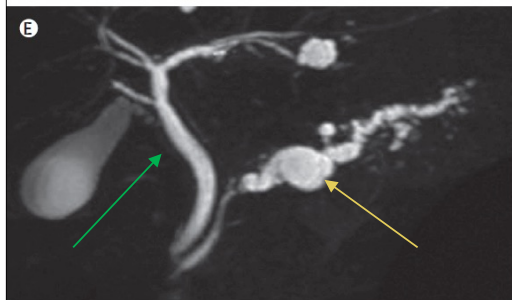
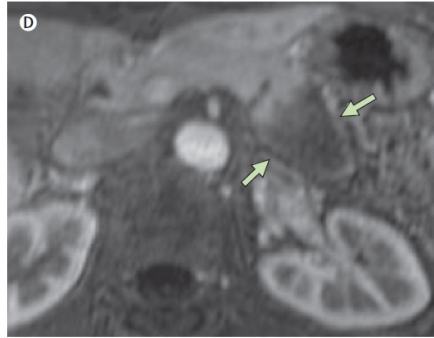
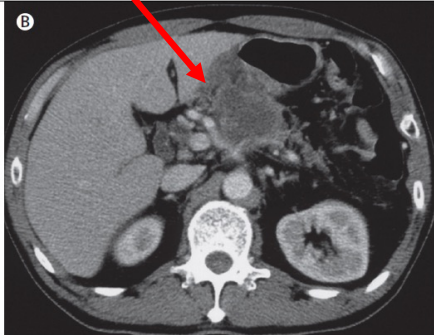


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- ❖ Jaundice (yellow skin and eyes, dark urine)
- ❖ Upper abdominal pain
- ❖ Mid back pain
- ❖ Nausea and vomiting
- ❖ Weight loss
- ❖ Loss of appetite (“anorexia”)
- ❖ Feeling full quickly (“early satiety”)
- ❖ Lethargy

DIAGNOSING PANCREAS CANCER

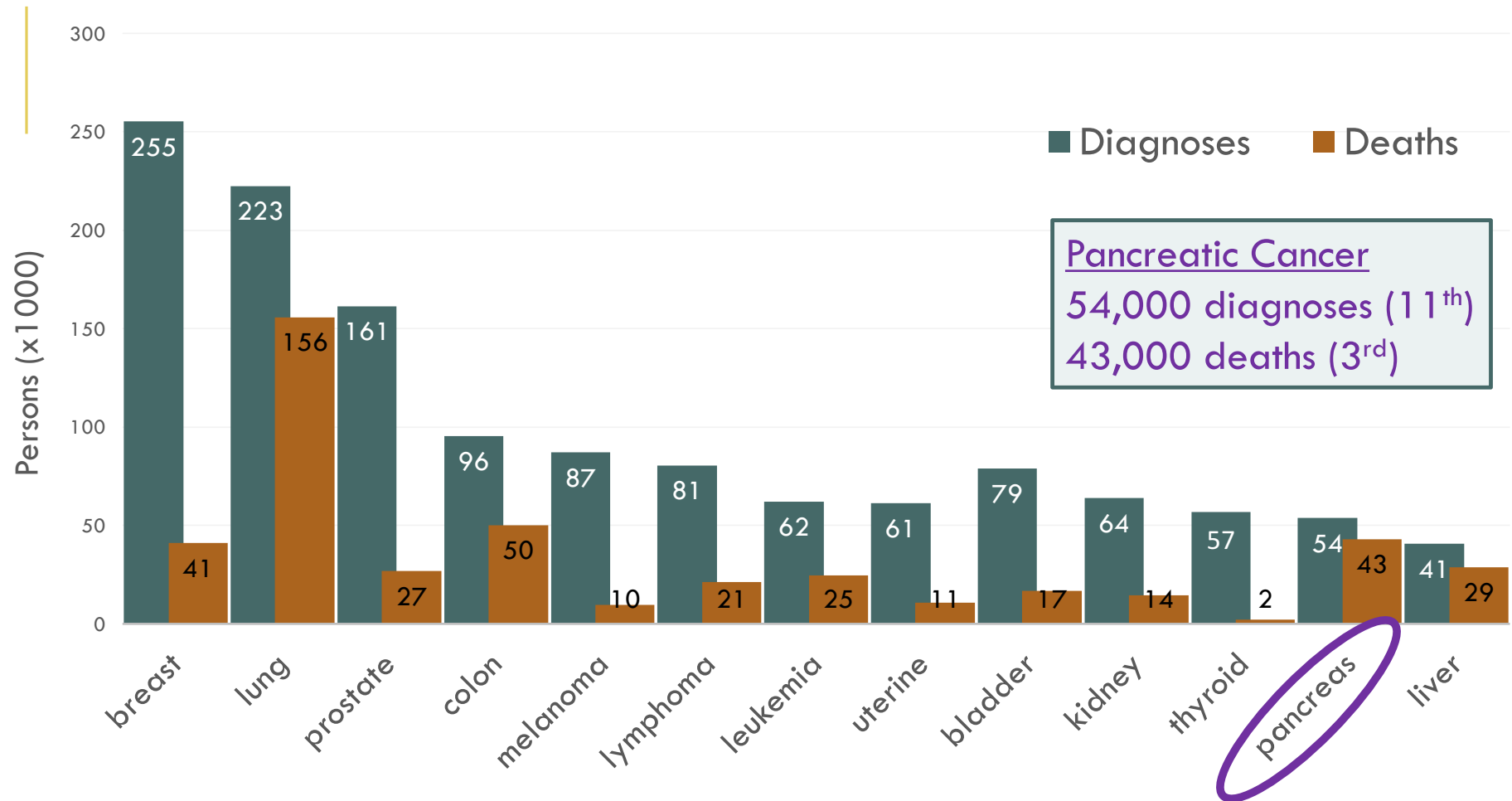
1. CT or MRI imaging



2. Biopsy:

- Endoscopic ultrasound (EUS)
- Percutaneous liver biopsy
- Surgical

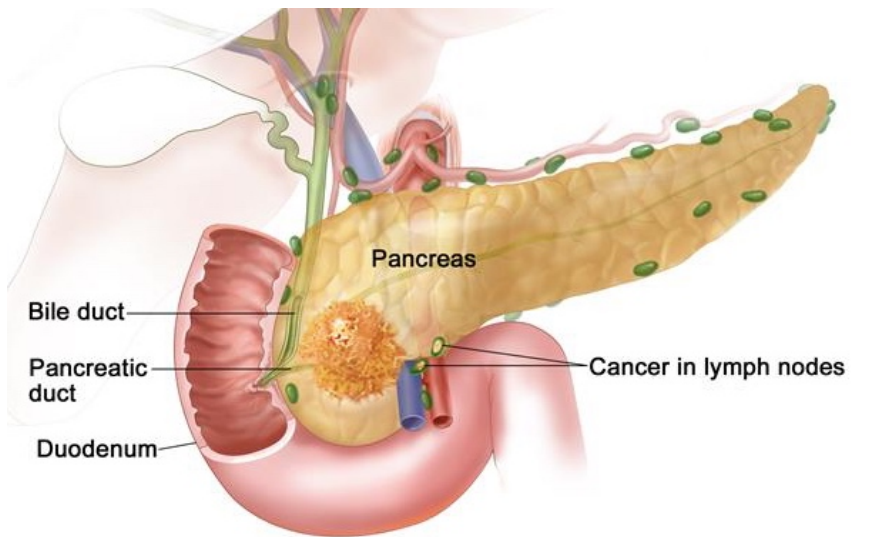
2017 PROJECTED CANCER RATES



American Cancer Society, *Cancer Facts and Figures 2017*

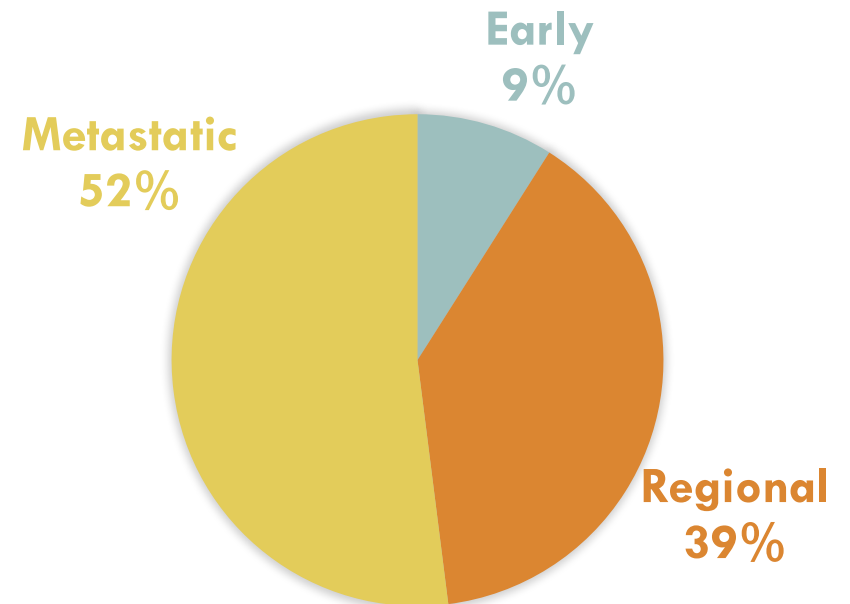
STAGE AT DIAGNOSIS

Most patients have metastatic disease at diagnosis



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Image from NCI PDQ and captured from:
<http://www.netwellness.org/healthtopics/pancreatic/pancreaticcancerstagesimages.cfm>






American Cancer Society, *Cancer Facts and Figures 2017*

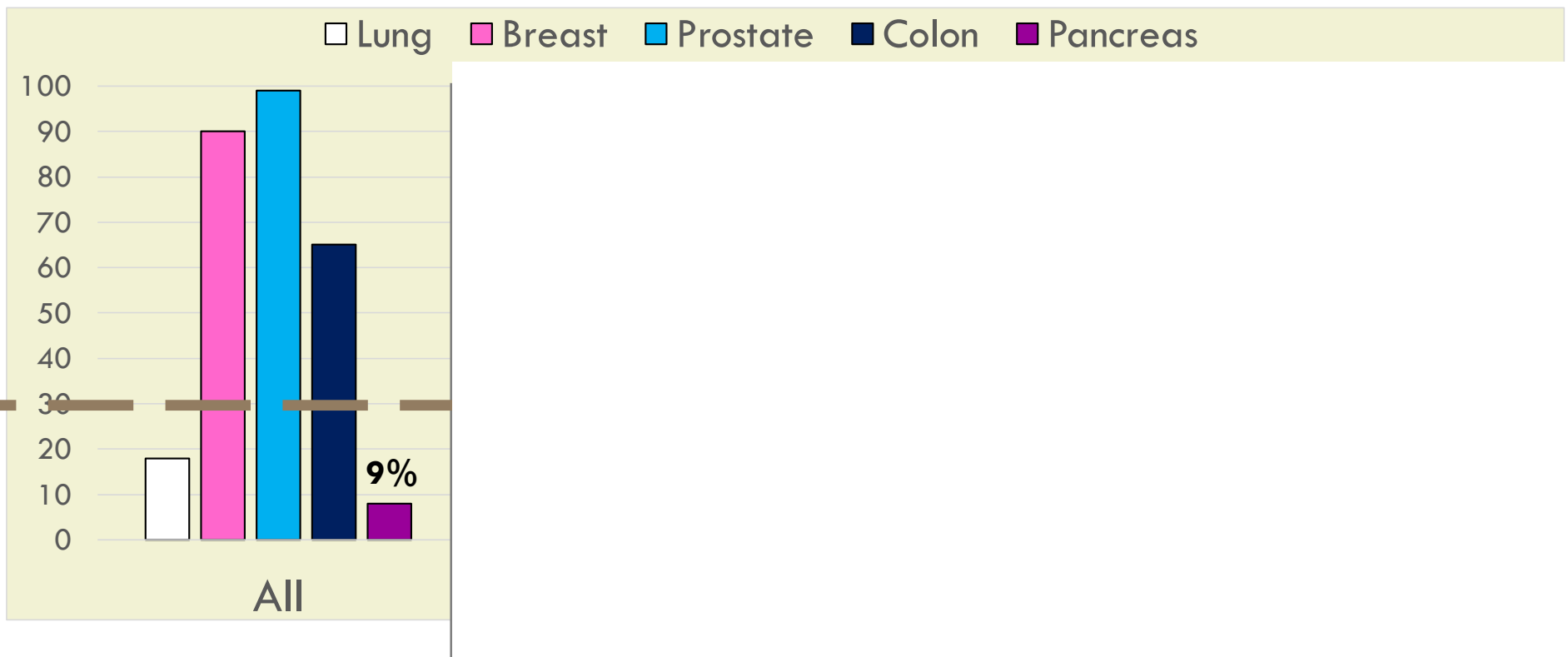
BARRIERS TO EARLY DETECTION

- ❖ Early symptoms are generic (“non-specific”)
- ❖ Current imaging methods rarely detect small lesions
- ❖ Difficulty in identifying specific biomarkers
 - ❖ Pancreatic Cancer is relatively rare (12.1 / 100,000 persons)
 - ❖ Test with 100% sensitivity and 99% specificity => 83 false positive for every real case
- ❖ Retroperitoneal positioning of the pancreas makes biopsy difficult

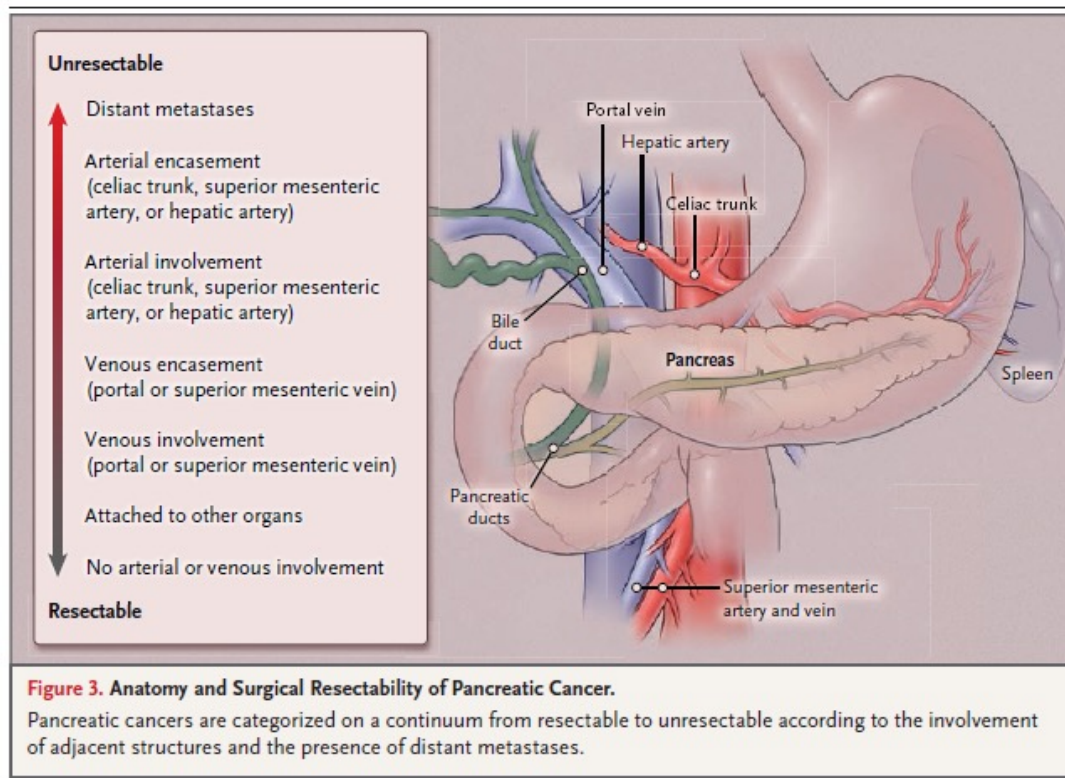
STAGE AT DIAGNOSIS

		Stage	Extent of Disease
“Early” (Curable)		I	Tumor confined to the pancreas
		II	Resectable but tumor extends beyond pancreas or lymph nodes involved
“Locally Advanced”		III	Tumor in the pancreas is not resectable but no spread to distant organs
“Metastatic”		IV	Spread to distant organs

5-YEAR SURVIVAL % BY STAGE

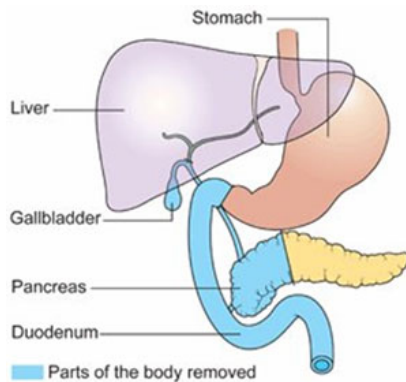


EARLY STAGE DISEASE: SURGERY + CHEMOTHERAPY



Surgical resectability is defined by degree of vascular involvement

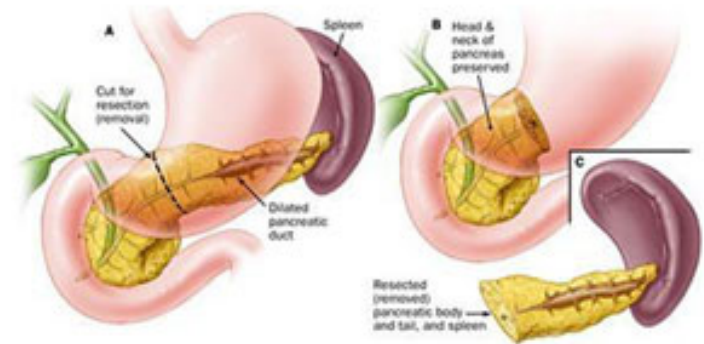
EARLY STAGE DISEASE: SURGERY + CHEMOTHERAPY



1. Whipple

- For tumors in pancreatic head
- Very complicated procedure
- High morbidity and mortality rate
 - Delayed gastric emptying (21%)
 - Fistula (15%)
 - Wound infection (11%)
 - Bleeding (2%)
 - Chyle leak (1%)
 - Cardiac event (3%)
 - Pneumonia (2%)
- Long recovery period
- Long-term complications

2. Distal Pancreatectomy

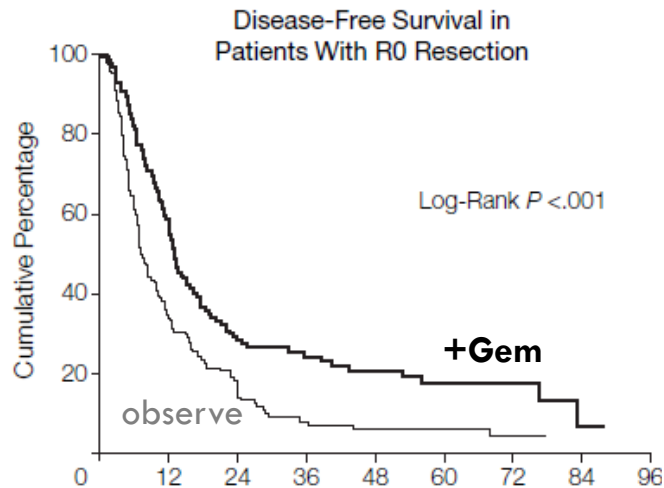


3. Total Pancreatectomy

- Results in insulin dependence

EARLY STAGE DISEASE: SURGERY + CHEMOTHERAPY

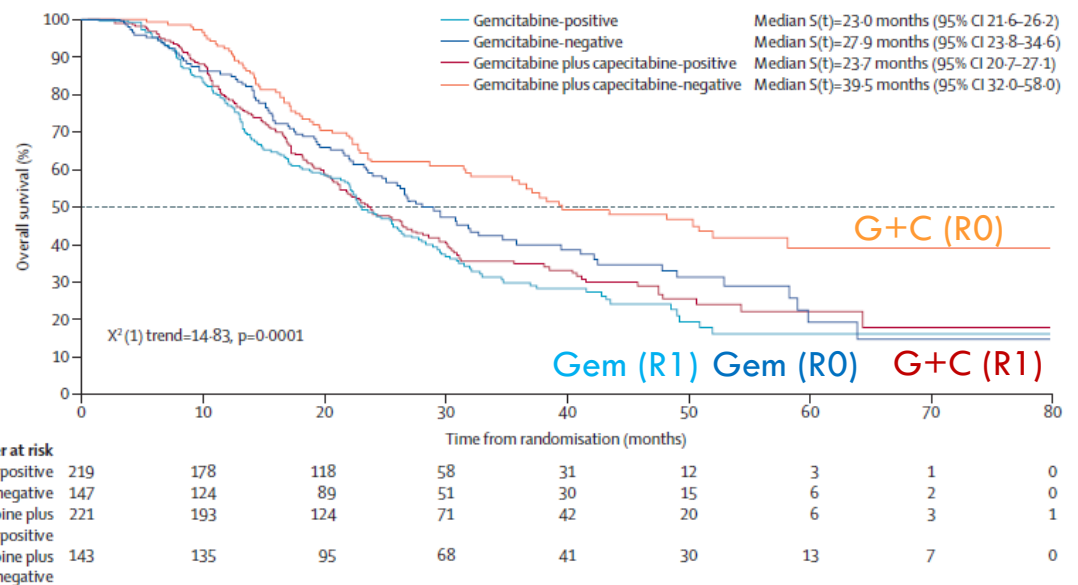
CONKO-001



No. at Risk								
Gemcitabine	145	78	33	21	14	9	6	1
Observation	148	49	23	9	6	6	2	0

Oettle et al, *JAMA*, 2007

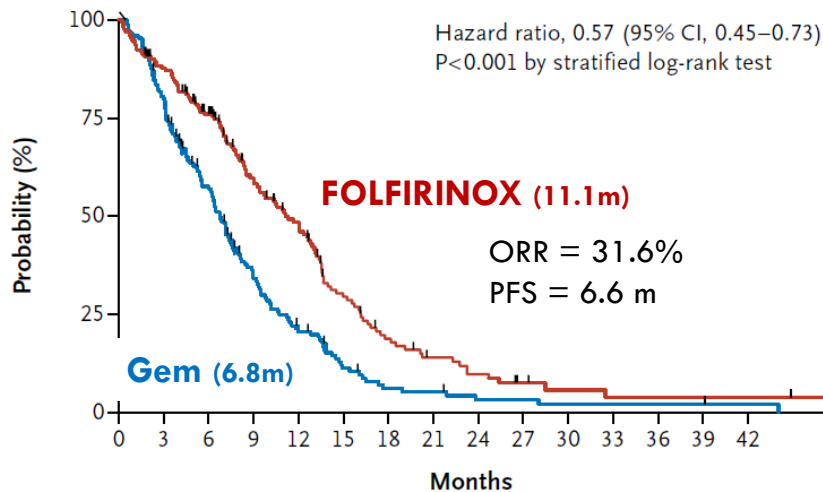
ESPAC-4



Neoptolemos et al, *Lancet*, 2017

STANDARD TREATMENTS FOR ADVANCED DISEASE

Overall Survival



No. at Risk

Gemcitabine	171	134	89	48	28	14	7	6	3	3	2	2	2	1
FOLFIRINOX	171	146	116	81	62	34	20	13	9	5	3	2	2	2

Chemotherapy:

- ❖ FOLFIRINOX
- ❖ Gemcitabine + NAB-paclitaxel
- ❖ Gemcitabine + erlotinib
- ❖ Gemcitabine
- ❖ 5-FU or capecitabine
- ❖ Capecitabine + liposomal irinotecan

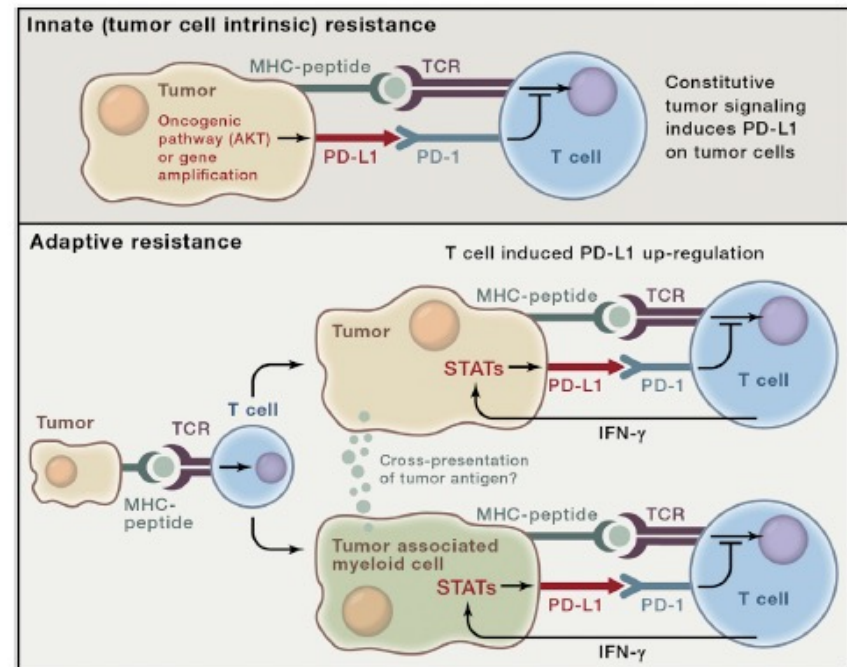
PROMISE OF NEW TREATMENTS?

No efficacy of targeted therapies +/- gemcitabine.



Cowley et al, *J. Hepatobiliary Panc. Sci.*, 2013

No efficacy with immune checkpoint inhibitors



Topalian et al, *Cancer Cell*, 2015

PALLIATING SYMPTOMS OF PANCREATIC CANCER

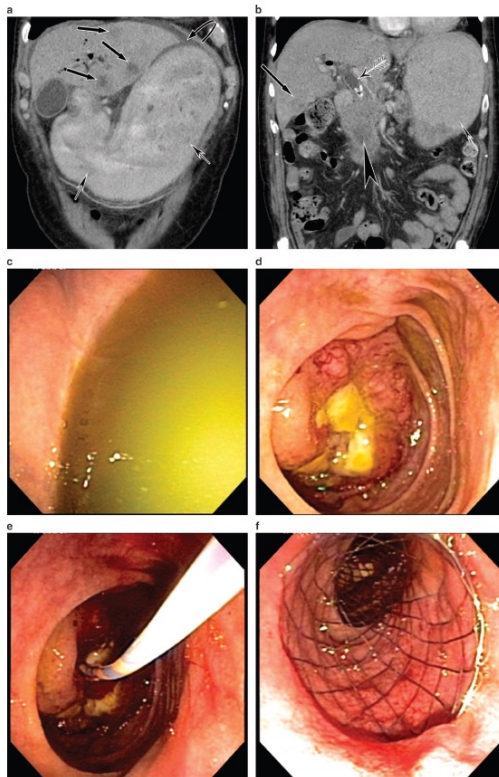


Figure 8. This patient with metastatic pancreas cancer presents with nausea and vomiting. (a) Computed tomography (CT) scan reveals liver metastases and a distended stomach. (b) CT scan reveals the pancreas mass, a dilated bile duct with stent in place, liver metastasis, and a distended fluid-filled stomach. (c) Endoscopic image of the fluid-filled stomach. (d) Duodenal obstruction by tumor. (e) Catheter and guidewire passage beyond the obstruction. (f) Duodenal stent placed.

Obstruction

- Biliary => jaundice
- Gastric or Duodenal => vomiting, poor nutrition

Pain

Weight loss and wasting syndrome

Nausea and vomiting

Poor appetite and feeling full quickly

Diabetes (“endocrine insufficiency”)

Fat soluble vitamin deficiency (“exocrine insufficiency”)

Blood clots

ON THE HORIZON

Stromal modulating agents

- PEGPH20
- FAK inhibitor

Immune therapy combinations

- Dual checkpoint inhibitor therapy
- +immune modulating agent
- +vaccine
- +oncolytic virus
- +radiation
- +drugs

Immune Cell Based Therapies

Current Phase III Treatment Studies

Advanced Dz

- Olaparib for germline BRCA mutant patients
- Gem + NAB-paclitaxel + PEGPH20
 - Pegylated hyaluronidase
- Gem + NAB-paclitaxel + napabucasin
 - STAT3 inhibitor
- Gem + Cape + GV1001
 - Telomerase peptide vaccine
- Gem + NC-6004
 - Micellar cisplatin formulation

Adjuvant

- FOLFIRINOX/ FOLFOXIRI
- Gem + NAB-paclitaxel

SUMMARY OF PANCREATIC CANCER

3rd leading cause of cancer death in United States because

- Many patients are diagnosed at a late stage
- Our treatments for early stage disease are not as effective as those available for other tumor types

Early diagnosis is difficult

Pancreatic cancer surgeries are very tough

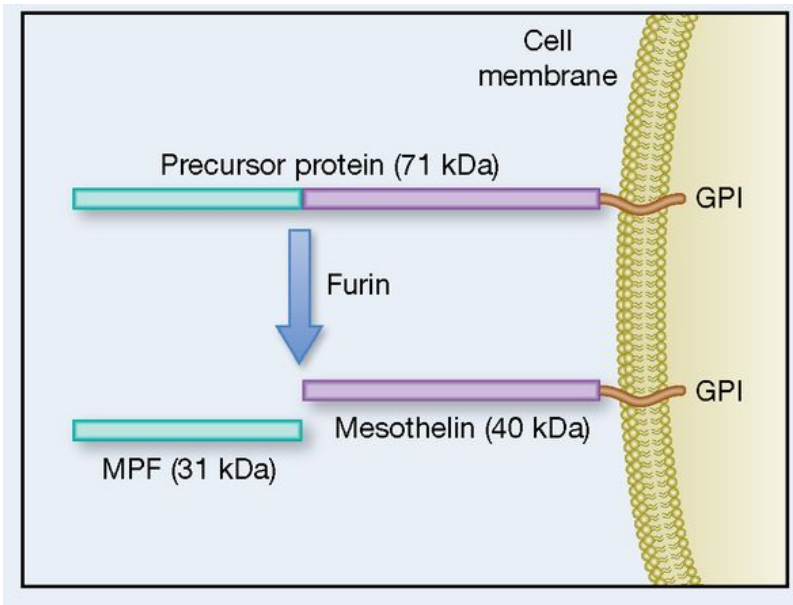
Available drug treatments are relatively ineffective

Many new treatments are currently under investigation

Side effects of pancreatic cancer and its current treatments have significant impact on patient quality of life

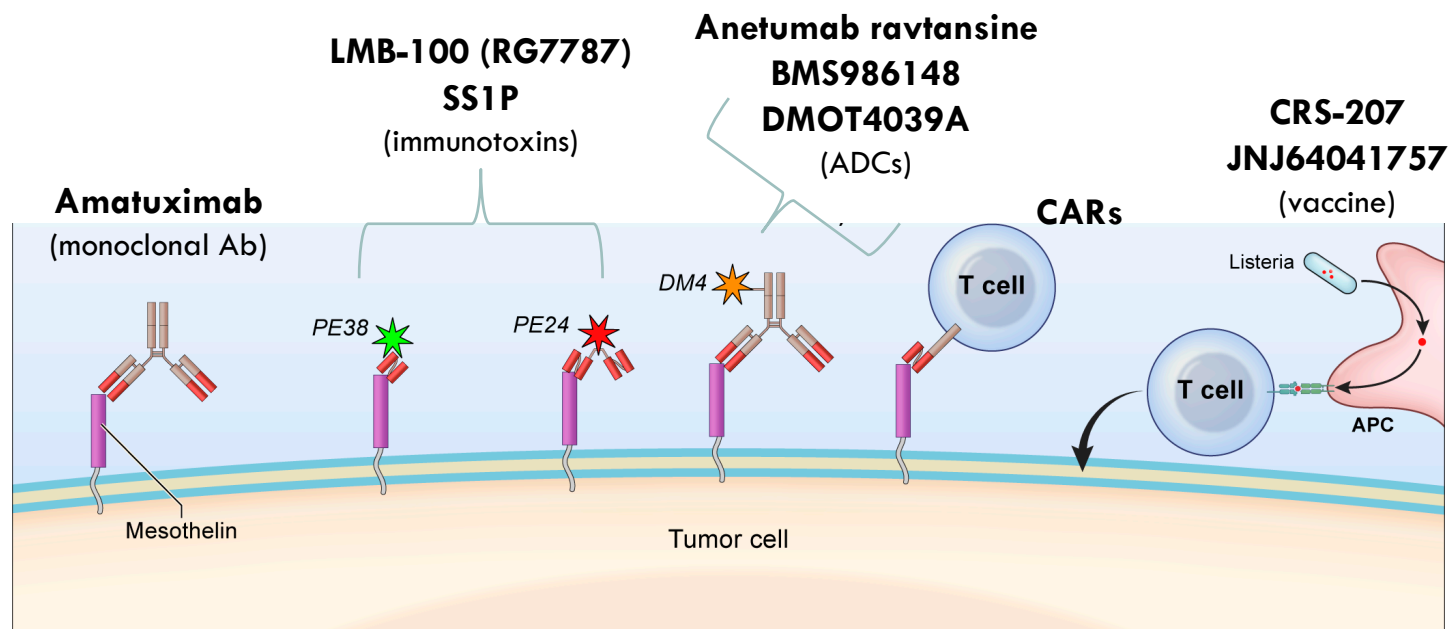
MY RESEARCH: MESOTHELIN-TARGETED THERAPY FOR PANCREATIC CANCER

Hassan et al. Clin. Cancer Res., 2004



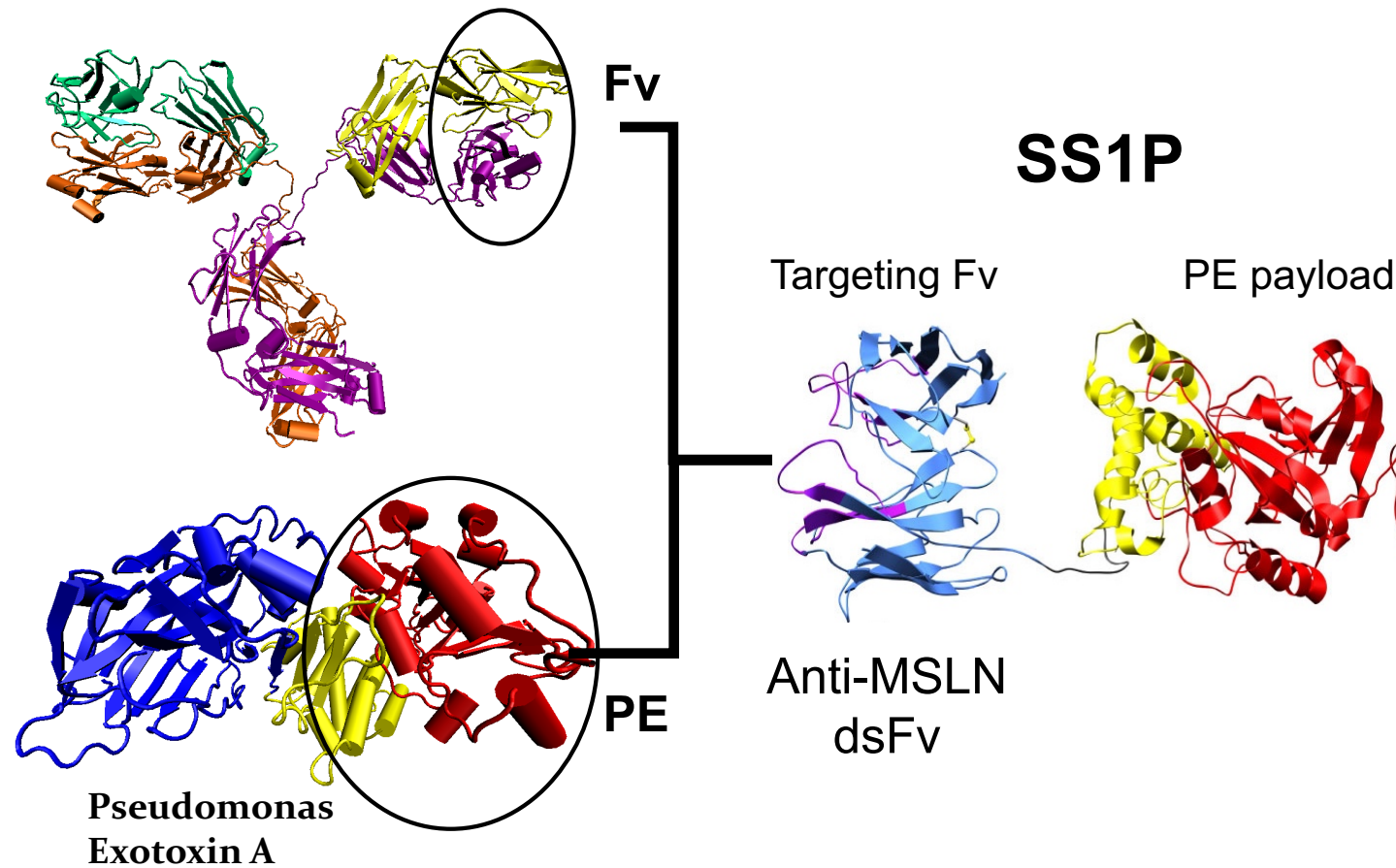
- Cancer-specific surface antigen expressed by many solid tumors
 - Mesothelioma
 - Pancreatic (95% have it)
 - Ovarian
 - Lung
 - Gastric
 - TNBC
- Normal expression limited to cells that line lung, heart and abdominal cavity

MSLN-TARGETED THERAPEUTICS IN THE CLINIC

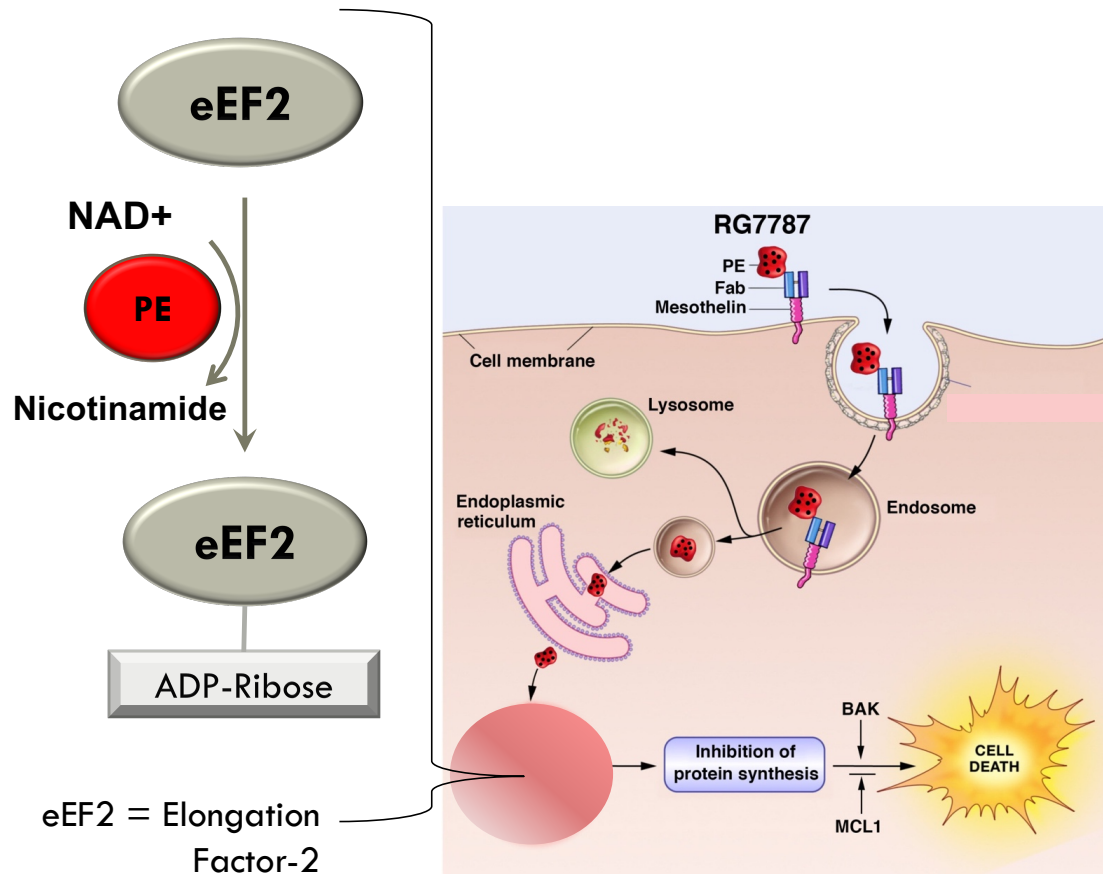


Adapted from R. Hassan et al., *in press J. Clin. Onc.*

RECOMBINANT IMMUNOTOXIN (RIT)



RECOMBINANT IMMUNOTOXINS

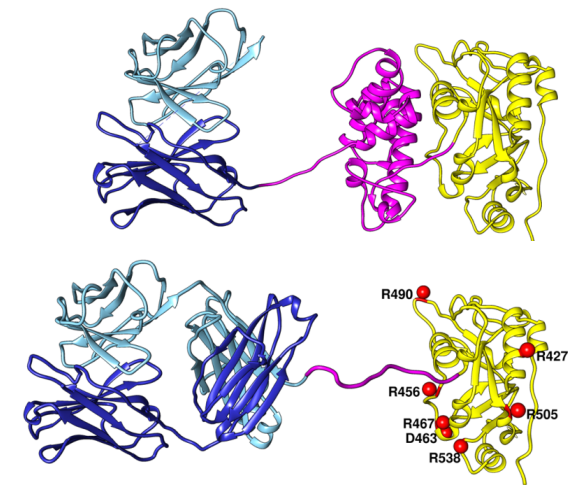


SS1P

LMB-100
(RG7787)

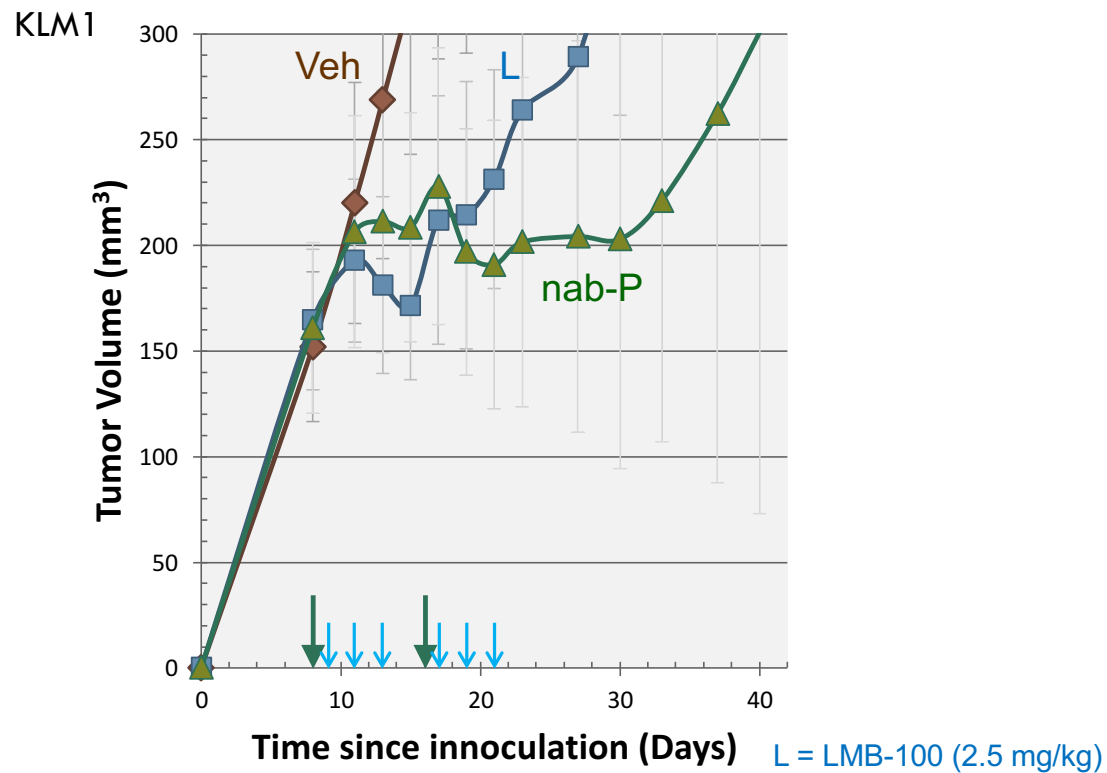
Anti-MSLN

Toxin Payload

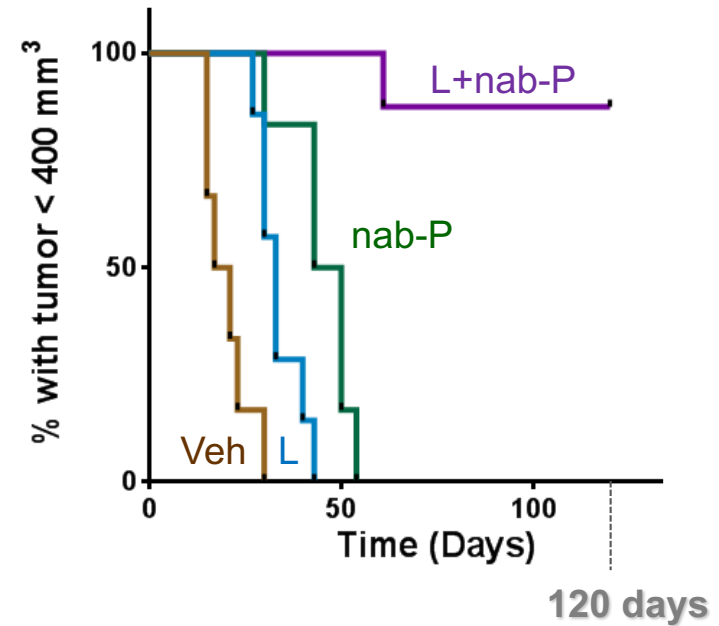
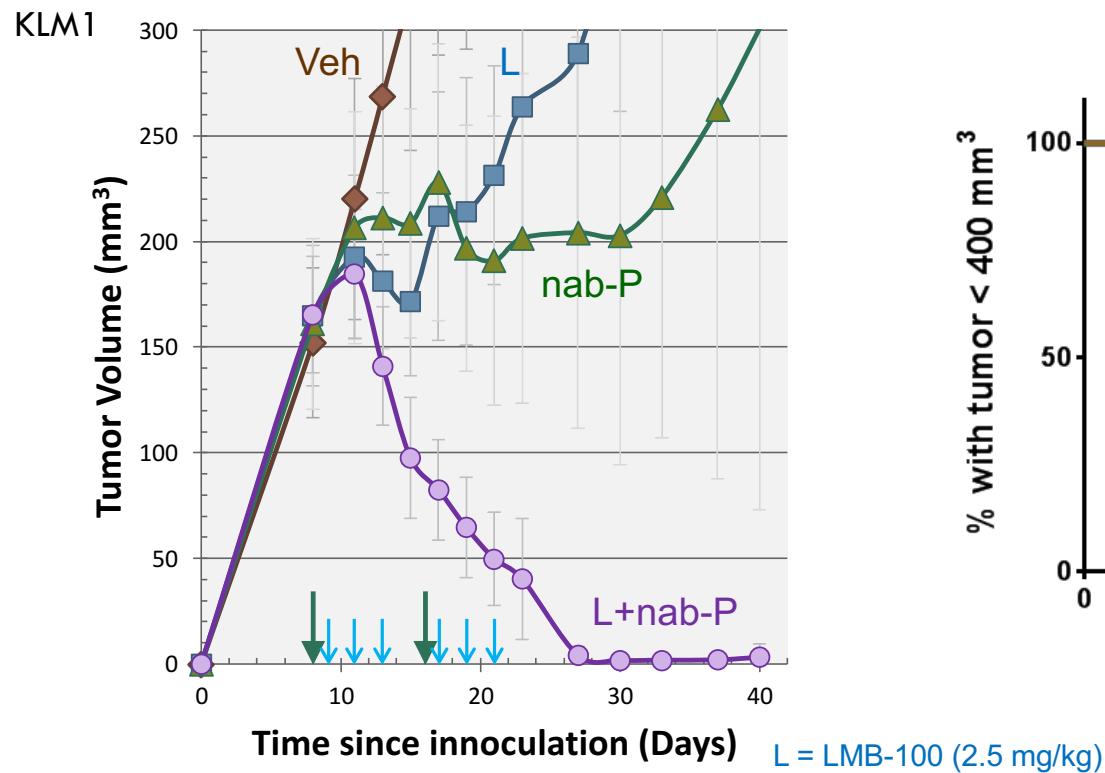


Mechanism of Action
Inhibits protein synthesis

LMB-100 WORKS WITH NAB-PACLITAXEL TO ELIMINATE PDAC TUMORS



LMB-100 WORKS WITH NAB-PACLITAXEL TO ELIMINATE PDAC TUMORS



PHASE IB/II: LMB-100 WITH NAB-PACLITAXEL FOR PREVIOUSLY TREATED ADVANCED PANCREATIC CANCER

Primary Goals:

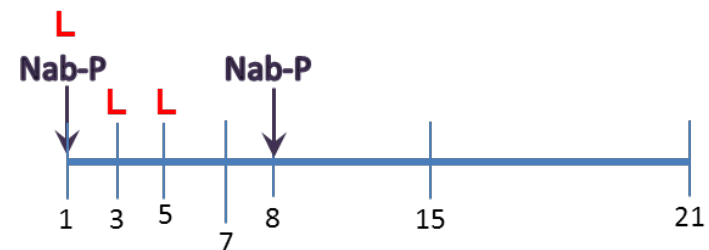
- Assess safety of the combination
- Determine whether the combination can shrink tumors better than nab-paclitaxel alone

Additional Goals:

- Assess immunogenicity of LMB-100
- Monitor how fast the body processes LMB-100
- Identify a mechanisms for the major toxicity of immunotoxins (vascular leak syndrome)

Cycle 1-4

(21 days)



L = LMB-100; **Nab-P** = NAB-paclitaxel

ACKNOWLEDGEMENTS



- **Alewine Lab:**
 - Michael Rudloff
 - Xianyu Zhang
 - Salma El-Behaedi
 - Rakan Albalawy
 - Emily Kolyvas
 - Rebekah Landsman
 - Danielle Arons
- **TGIB Clinical Team**
 - **Yvonne Mallory**
 - **Lisa Bengtson**
 - Susan Sansone
 - Emerson Padiernos
 - Anish Thomas
 - Arun Rajan
 - Austin Duffy
 - Tim Greten
- **Ira Pastan**
- **Raffit Hassan**

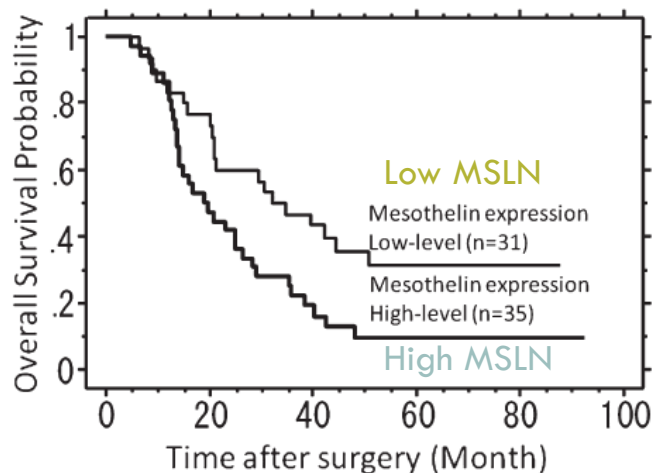




QUESTIONS?

BIOLOGICAL ROLE OF MSLN IN PANC CA

High expression prognostic for short survival in resectable patients



T. Einama et al, *Pancreas*, 2011

Table 3. Multivariate predictors of short-term survival. (<1yr)

Prognostic marker	OR	95% CI	P value
MSLN negative	Ref		0.01
MSLN 1+	1.65	(0.48, 5.72)	
MSLN 2+	2.64	(0.85, 8.22)	
MSLN 3+	12.47	(2.43, 64.14)	

J. Winter et al, *PLoSOne*, 2012

MSLN EXPRESSION IN PANCREAS CANCER

(C) Pancreatic ductal adenocarcinoma (5B2 antibody)

Negative	1+ (1-25% cells) ^{\$}	2+ (26-50% cells)	3+ (>50% cells)	Total	Reference
0/60	10/60	50/60		60/60 (100%)	Argani <i>et al.</i> (5)*
0/14	3/14	5/14	6/14	14/14 (100%)	Frierson <i>et al.</i> (2)* ^{\$}
1/11	0/11	2/11	8/11	10/11 (91%)	Ordenez (6)*
2/14	0/14	3/14	9/14	12/14 (86%)	Ordenez (1)*
7/68	22/68	39/68		61/68 (90%)	Swierczynski <i>et al.</i> (7)* [#]
0/18	2/18	1/18	15/18	18/18 (100%)	Hassan <i>et al.</i> (8)*
10/185 (5.4%)	37/185 (20%)	138/185 (75%)		175/185 (95%)	Total prevalence

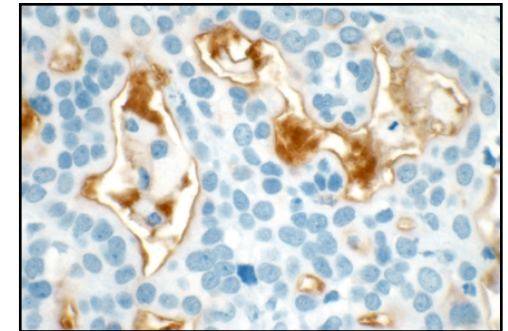
* 1% cutoff. ^{\$}1+ was instead defined as focal (1-10% cells only) by Frierson *et al.* (2)

[#]Swierczynski *et al.* (7) demonstrated 10% of positive PDAC tumors could be missed in TMAs versus whole sections due to focal mesothelin staining.

5%
Neg

20%
Low

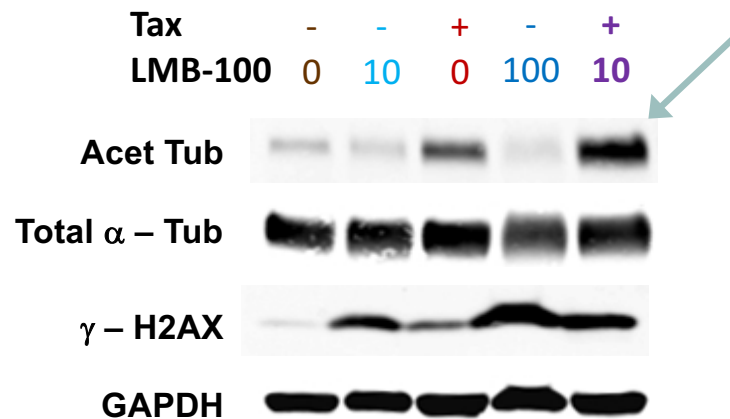
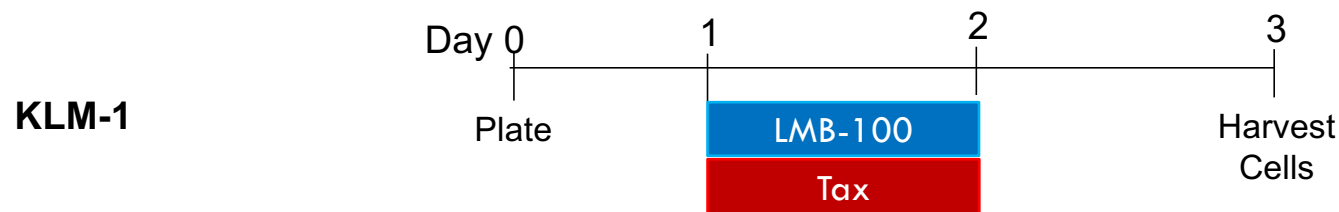
75%
Good to High



Hassan *et al.* Clin. Cancer Res., 2004

Scales *et al.*, Mol. Cancer Ther., 2014

ADDITION OF LMB-100 ENHANCES TAXANE ACTIVITY PRIMES TUMOR CELLS FOR APOPTOSIS



Survival 5 Years From Diagnosis

Early	29%
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Regional	11%
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Metastatic	3%
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All	8%
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